Paper

AN INVESTIGATION INTO THE PREVALENCE OF THYROID DISEASE ON KWAJALEIN ATOLL, MARSHALL ISLANDS

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Abstract—The prevalence of thyroid nodules and thyroid cancer was studied in the indigenous population residing on Ebeye Island, Kwajalein Atoll, in the Republic of the Marshall Islands. This island, centrally located in the nation, is home to about 25% of the nation's population, many who have migrated there from other atolls. The objective of the study was to obtain thyroid disease rate statistics on as much of the population as possible that was alive during the years of nuclear testing and to test the hypothesis that described a linearly decreasing prevalence of palpable nodules with increasing distance from the Bikini test site. 1,322 Marshallese born before 1965 were given a thyroid examination using neck palpation, fine needle aspiration biopsy, and high resolution ultrasound imaging. Approximately 40% of the total population living on this island who are at risk from exposure to radioactive fallout during the years 1946–1958 were screened. Of that group, 815 were alive at the time of the BRAVO test on 1 March 1954. Two hundred sixty-six people with thyroid nodules were found (32.6%): 132 were palpable nodules (16.2%), and 134 were nodules that could be diagnosed with ultrasound only (15.7%). Prevalence of palpable nodules was particularly high in men and women older than 60 y, in men who were 6 to 15 y of age at the time of the BRAVO test, and in women 1 to 10 y of age at the time of the BRAVO test. In 22 people, the clinical diagnosis was most likely cancer though histopathological evidence was only available from 11 operated cases. Of the 11 operated cases, 10 were cancer. Cancer prevalence was particularly high in those women born between 1944 and 1953 (7/220 = 3.2%), i.e., who were children during the early years of nuclear testing. The Ebeye data showed a marginally significant correlation between palpable nodule prevalence among women and distance to Bikini ($r = -0.44$, $p = 0.06$). This report summarizes the clinical findings of the thyroid examinations, the age distributions for nodular disease and cancer, and examines the relationship between prevalence of nodules and present day levels of ^{137}Cs in the environment of each atoll.

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INTRODUCTION

THE U.S. atomic weapons testing program in the Pacific conducted between 1946 and 1958 resulted in contamination of a number of atolls in the Marshall Islands to various degrees (Simon and Graham 1997). The most serious radiation exposures were caused by early radioactive fallout from the test, Castle BRAVO, a hydrogen bomb detonated on Bikini Atoll on 1 March 1954. The radioactive fallout was intense on the inhabited atoll of Rongelap (175 km to the E of Bikini) resulting in thyroid exposures estimated between 10 and 40 Gy for an adult and between 50 and 200 Gy for a 1-y-old child (Lessard et al. 1985). Lower exposures were received on the atolls of Ailinginae (about 30% of the value at Rongelap) and Utrik (about 10% of the value at Rongelap). The exposed communities on these three atolls were evacuated, treated for acute radiation illness, and provided with follow-up medical care and cancer surveillance over the decades since (Conard 1984; Adams et al. 1989). The most significant long-term health effect in the exposed population was an increased frequency of thyroid nodular disease including thyroid cancer, which has been attributed to intake of short-lived radioiodines immediately following the BRAVO detonation.

There is historical evidence to indicate that residents of other atolls may have been exposed to radioactivity in local fallout from the BRAVO test as well as from other explosions. In particular, fallout data were collected on Kwajalein Atoll (located about 400 km SE of Bikini) using gummed film as part of the worldwide fallout monitoring network of the AEC Health and Safety Laboratory. Gummed film data (measurements of beta activity collected within successive 24-h periods) during the years 1954 through 1958 (Harley et al. 1960) show that all eighteen of the large Marshall Islands tests (those >1 MT explosive yield) were detected at Kwajalein at about 100 × the background radiation level (Simon and Graham 1996). Presumably, other mid-latitude atolls in the Marshall Islands received similar amounts of early fallout as did Kwajalein.

The contamination on all of the atolls, consisting of mainly ^{137}Cs, has recently been assessed by the Marshall Islands Nationwide Radiological Study and reported (Simon and Graham 1994, 1997) including calculations of external exposure-rates and ingestion doses under various dietary scenarios. The radiological data indicate that 10 of the 24 inhabited atolls or separate reef islands have environmental levels of ^{137}Cs enhanced over the level of global fallout received in the mid-Pacific region. Many of these locations are only minimally enhanced in ^{137}Cs, which has not contributed any dangerous exposure over recent decades. However, the extent of exposure of the Marshall Islands population to radioiodine during the testing years has never been assessed. Moreover, little information exists about health consequences among residents of the many atolls other than Rongelap and Utrik.

Only a single health effects study prior to this one examined Marshallese at numerous locations from around the Marshall Islands. In a report by Hamilton et al. (1987) it was suggested that thyroid nodular disease, as diagnosed by palpation of the neck, was frequent in residents of many atolls from throughout the Marshall Islands. In that study, an increased prevalence was noted at distances closer to the Bikini test site with a linear decrease in prevalence with increasing distance. The Nationwide Radiological Study (Simon and Graham 1996) and a Marshall Islands Government appointed Advisory Panel (McEwan et al. 1997) recommended to the Marshall Islands Government in 1990 that an independent thyroid screening study should take place and that the hypothesis of Hamilton be independently tested. Subsequently, a nationwide thyroid disease screening program was initiated to gather data useful for such an evaluation and also for the purposes of advising the Marshall Islands government on the current health situation with respect to thyroid disease. Of all the conditions for which claims for damages are made to the Marshall Islands Government, thyroid disease is the most common and for that reason it is of interest to the Ministry of Health.

The specific objectives of the thyroid disease screening program were (1) to examine and gather data on the frequency of thyroid disease (both nodular and cancerous conditions) and information about the subjects residence history in as large of proportion as possible of those Marshallese alive at the time of the BRAVO test and during the years of atomic testing, (2) to advise the Government of the Marshall Islands on the findings from the medical screening program, and (3) to test the hypothesis of Hamilton. The long term goals of the investigators also include estimating thyroid radiation exposures using historical and contemporary data, though those analyses are still underway and are beyond the scope of this report. The objective of this paper is to report a summary of the medical findings from examinations conducted on Kwajalein Atoll from January to March 1993 and during follow-up examinations in 1996 and the results of statistical hypothesis testing of the Hamilton hypothesis using the thyroid screening data.

METHODS

Location and study population

Most of the thyroid examinations were conducted in the Ebeye Hospital, located on Ebeye Island in Kwajalein Atoll. Kwajalein, the largest atoll in the world, is centrally located in the Marshall Islands about 400 km SE of Bikini Atoll and is used as an U.S. Army missile test range. Ebeye Island is located about 15 km N of the Army base, which is the southern most island in the atoll. Ebeye is home to over 12,000 Marshallese, about one fourth of the total Marshall Islands population today. The population of Ebeye is known from national census data to be a mixture of former residents of atolls that are located over the entire geographic range of the Marshall Islands. Many of the people examined in Ebeye also lived there at the time of the BRAVO test. The remaining persons lived on 20 other atolls. Because Ebeye has jobs, goods and services not existent on more remote atolls, many Marshallese have migrated there for semi-permanent or permanent residence. The population of Ebeye includes Marshallese from a variety of locations throughout the chain of atolls; therefore, it provided an excellent location for the first phase of thyroid examinations.[§]

The main source of exposure of Marshallese is believed by many to have been the BRAVO test; hence, those Marshallese alive at the time of the test are usually considered most at risk for radiogenic disease. In the original design of this study, consideration was given to using Marshallese born within 10 y after the testing era as control subjects. They would be the only population available that had been screened for thyroid disease and were genetically and culturally similar to the exposed population. Though not a perfect control group because of differences in age, subjects who were born up through the 10-y period following the testing era, i.e., with dates of birth before 1968, were originally invited for examination. Although we sought persons in the age range described, we did not reject anyone requesting a thyroid examination.

After the original study design was implemented, historic deposition data were located that influenced our choice of primary study cohort. The gummed film data collected during the Castle and Ivy series (1954–1958) indicated there had been deposition of regional fallout on Kwajalein from other large tests in the Marshall Islands, thereby suggesting that Marshallese might have been exposed from events other than BRAVO. Consequently, all Marshallese who had already been examined and who were *in-utero* or alive any time during the weapons testing years, i.e., before the last test on 11 August 1958, were considered at risk. The primary analysis reported here, however, is for the cohort alive at the time of the BRAVO test (termed as the Ebeye "BRAVO cohort") so that a comparison can be made with the study by Hamilton et al. (1987). We have defined a group of secondary interest as all those Marshallese who were born before 1 March 1959. We have termed this group the "End of testing" cohort or EOT cohort. Finally, those

[§] A second phase of thyroid examinations were held in 1994 in Majuro, the capital city, however, those data are not reported here. The second phase of examinations should not be confused with the follow-up examinations of the Ebeye population in 1996 which are discussed in this paper.

individuals who presented themselves for examination but who were born between 1 March 1959 and 31 December 1964, were termed the Ebeye "After testing" cohort or AT cohort.

It was of interest in this study to attempt to determine if there was a relationship between prevalence among residents of each atoll at the time of the testing and the location of residences. Because the testing period lasted for 12 y, long enough to allow families to move among locations, the issue of residence and exposure is complex and requires a complete residence history and dose reconstruction for each subject. Although such work is in progress, in this report only the residence at the time of the BRAVO test is examined and all analyses are conducted with respect to that residence location. The rationale behind this methodology is to make this comparison as consistent as possible with the methods of Hamilton et al. (1987). In that study, residence location was used as proxy variable for exposure to short-lived radioiodines.

Examinations

The thyroid screening investigation was composed of two components: a personal interview and a clinical examination. The interview was conducted by Marshallese assistants in their native language. The most important data collected in the interviews were a complete residence history from birth until the examination date, a brief health history, a fertility history for women, and brief data on food and diet preferences. The residential history data were collected with the intent of later using them in calculations to determine radiation exposure.

Each study subject was examined sequentially by two endocrine surgeons highly trained in the use of ultrasound and palpation. Each physician administered either a palpation or ultrasound exam, and each was initially blinded to the findings of the other as well as to the interview findings. Physicians alternated in their assignment to perform ultrasound or palpation.

The physical examination performed by one of the two doctors included a brief medical interview (with the help of a translator), blood pressure measurement, and a careful palpation of the neck. The second doctor performed the ultrasound examination of the neck.[||] An initial diagnosis was made in real-time. In addition, a minimum of four pictures of the echograms of each participant were recorded. When thyroid nodules were found, additional pictures were taken and the size of each nodule was measured in three dimensions. Our definition of a nodule as imaged by ultrasound included all focal abnormalities of the echo pattern that were larger than 2 mm in diameter though the minimum nodule size that could be reliably detected was 4 mm.

The involvement of two physicians sometimes resulted in differences between the clinical and ultrasound findings. When such differences occurred, it was the policy of the study for the doctors to discuss their findings and to re-examine the neck of the patient again in an effort to reach a consensus diagnosis.

Every participant who had a palpable thyroid nodule was told in the Marshallese language that he or she had a nodule and that a fine needle aspiration (FNA) biopsy was recommended to determine its nature. In the biopsies performed, only one puncture was made for each nodule using a disposable 21G needle with a 12 mL syringe. Because many subjects feared the pain from the puncture, it was determined early in the study that multiple punctures would likely reduce community participation. For this reason, the biopsy was limited to a single puncture. The aspirated material was divided onto four slides and smeared. Two slides were stained with a modified Papanicolau method and the other two slides were stained with a modified Giemsa method. Staining was performed in Ebeye within 72 h after the biopsy. All slides were examined by (N. Kimura) in the Department of Pathology of Tohoku University (Sendai, Japan).

In January 1996, three years after the first examinations, a scheduled follow-up program was conducted in Ebeye. Every person who was diagnosed in 1993 with a palpable or non-palpable thyroid nodule was personally invited by letter and by local radio announcement to attend the follow-up clinic. Three goals were integral to the follow-up study: (1) to provide reassurance to those persons previously diagnosed of an abnormality that they were not left without proper surveillance and medical care; (2) to determine the progression or regression of thyroid nodules with an emphasis of examining the long-term behavior of non-palpable nodules; and (3) to verify the 1993 clinical findings to the degree possible, knowing that some nodules might have regressed while new ones might have appeared.

The follow-up examinations began with an interview by one of the investigators (KRT) using a Marshallese interpreter. Special emphasis was placed on the questions concerning the subject's residence history. The interview was followed by a clinical examination by two of the doctors from the 1993 exams (TT and NN) who are authors of this report.

All clinical techniques in 1996 were the same as in 1993, except for a modification of the policy with respect to FNA punctures. About 30% of the FNA biopsies in 1993 had not been successful because of insufficient cellular material. In 1996, a temporary cytology laboratory was set up in the examination room for the purposes of improving the rate of successful FNA biopsies. An experienced cytologist checked the quality of the FNA biopsy while the patient was still in the clinic and notified the physicians when it was not successful so that a second puncture could be made.

Statistical methodology

The crude and age-adjusted prevalence of all nodular goiters (nodular goiter and nodules are equivalent), and palpable nodules only, was estimated for each atoll based on the 1954 residence location of each study subject (see Table 1 for data from the Ebeye BRAVO cohort). Two standardization methods were used to

[||] Equipment used was an ALOKA echo camera SSD-121™ with a 7.5 MHz mechanical sector probe.

correct for differences in age-distribution between the groups: the direct and indirect methods. The estimates obtained by the direct method reflect the prevalence of nodular goiter in the index population when this index population has the same age distribution as the standard population. The age distribution of the entire population on the Marshall Islands, as taken from the national census (RMI 1989) was used as a standard. With indirect standardization, the age-specific prevalence rates of the standard population are applied on the age distribution of the index population. Since no external source was available, we took all the people born before 1 March 1954 and residing on those atolls southwards from Jabwat in 1954 as the reference population. These atolls were selected because the exposure of residents to radioactive fallout was likely the lowest there of all the atolls.

With the direct method, the number of people in each age group at each atoll of residence was often very small with the result that the age-specific prevalence rates were subject to large fluctuations. The use of the indirect standardization method also had its shortcomings because of the lack of a large reference population. In spite of that, we chose to use the indirect method because the age-adjusted prevalence rates showed less fluctuation in comparison to the crude prevalence rates.

Various hypotheses were tested using the results of both the screening data and the age-adjusted data. The null hypothesis of no difference in crude prevalence among the atolls (other than Rongelap and Utrik) was tested by a Chi-square test. In an examination of possible relationships between the age-adjusted rates and location of residence in 1954, the prevalence data were plotted against the distance between Bikini and the residence atolls. Correlations between prevalence and distance were examined. Because the population size in 1954 varied dramatically among the atolls, the reliability of the prevalence estimates also varied. Consequently, we weighted the prevalence estimates by the inverse of the group variance.

To examine the occurrence of nodular goiter in more detail, a logistic regression analysis was conducted using several variables as predictors: the distance from Bikini to the residence atoll, the variable θ—defined as the angle measured clockwise between a W to E line drawn through Bikini and a line from Bikini to the center of the residence atoll—sex, age and the interaction term defined by the product of distance and θ. The dependent variable was the presence or absence of nodular goiter in the individual. The data of distance and θ are given in Table 2.

We also examined the relationship between the age-adjusted prevalence and current data of the radiological conditions at each atoll. For this purpose, we used measurements of ^{137}Cs in the environment that were obtained during the years 1989 through 1994 by the Marshall Islands Nationwide Radiological Study (NWRS). These measurements were conducted on all islands of the nation at least 500 m in length in all of the 29 atolls as well as the 5 separate reef islands. The measurements included over 1,200 *in-situ* gamma spectrometry measurements, collection and laboratory analysis of more than 800 surface soil samples and more than 200 deep soil profiles. The results of the measurements were compared with the levels of global fallout estimated for mid-Pacific locations from published data on islands nearby to the Marshall Islands. This comparison provided a measure of the degree of ^{137}Cs contamination

Table 1. Summary of prevalence data of Ebeye BRAVO cohort grouped by atoll of residence in 1954.

Residence in 1954	Number of people	Mean age, y	Female %	Benign solitary nodules	Benign multiple nodules	Malignant goitre	Thyroid-ectomy	Crude %, all nodules	Age-adjusted %, all nodules	Crude %, palpable nodules only	Age-adjusted %, palpable nodules only
Wotho	7	55.7	57.1	2	0	0	0	28.6	24.3	14.3	12.8
Rongelap	11	52.9	54.5	1	0	0	4	45.5	40	36.4	31.4
Ujae	30	47.8	50	6	0	1	1	26.7	26.4	13.3	11.3
Lae	23	50	52.2	7	2	0	1	43.5	46.6	26.1	24.5
Kwajalein	346	53.3	57.8	89	26	10	4	37.3	34.5	18.5	18.9
Likiep	52	50.8	55.8	9	2	0	0	21.6	20.7	13.5	13.8
Namu	17	50.7	58.8	3	0	0	0	17.6	17.9	5.9	5.7
Utrik	14	48.2	64.3	4	1	0	1	42.9	44.7	35.7	39
Ailuk	14	48.2	64.3	3	0	0	0	21.4	22.2	7.1	6.1
Wotje	17	51.7	88.2	5	1	0	0	35.3	32.4	17.6	16.9
Ailinglaplap	77	50.3	58.4	21	2	0	1	31.2	29.8	13	12.9
Mejit	20	50.2	55	6	0	0	0	30	28.3	5	4.7
Maloelap	15	50.5	46.7	1	1	0	0	13.3	13.5	6.7	7.3
Namorik	17	46.1	52.9	0	1	0	0	5.9	6.6	5.9	6.2
Aur	10	47.2	40	0	0	0	0	0	0	0	0
Jaluit	47	48.5	68.1	5	5	1	1	25.5	27.8	12.8	14.5
Kili	1	43	100	1	0	0	0	100	n/a	0	0
Majuro	55	50.9	61.8	21	4	2	1	50.9	46.8	20	19.2
Arno	10	44.8	40	2	0	0	0	20	19.9	0	0
Ebon	28	45.3	64.3	5	0	1	1	25	27.3	14.3	14.4
Mili	4	44.8	75	0	0	0	0	0	0	0	0
Total	815	51.11	58.5	191	45	15	15	32.6	n/a	16.2	n/a

Table 2. Atolls of residence in 1954 for subjects in Ebeye BRAVO cohort and Hamilton study and related information used in hypothesis testing and Figs. 1 and 4.

Number	Atolls represented in Ebeye study	Atolls in Hamilton study	Distance from Bikini (km)	Angle θ (°)	Ratio total ^{137}Cs:global fallout ^{137}Cs
1	Ailinglaplap		574	51	1.25
2	Ailuk	√	505	15	8.15
3	Arno		833	35	1.6
4	Aur		731	29	1.3
5	Bikini		0	0	1235
6	Ebon	√	855	64	1.1
7	Enewetak		350	177	295/975
8	Jaluit	√	769	52	1.2
9	Kili		770	57	1.2
10	Kwajalein	√	401	49	2.0[a]
11	Lae	√	305	74	1.65
12	Likiep	√	453	24	5.8
13	Majuro		813	38	1.2
14	Maloelap	√	683	25	1.4
15	Mejit	√	609	12	7.35
16	Mili	√	918	39	1.65
17	Namorik		722	65	1
18	Namu		463	54	1.4
19	Rongelap	√	175	10	210[b]
20	Ujae	√	262	85	1.15
21	Ujelang		537	157	2.55
22	Utrik	√	472	3	16
23	Wotho	√	162	70	2.25
24	Wotje	√	568	24	2.85

[a] North Kwajalein 2.1–4.3, South Kwajalein 1.0–2.0; value of 2.0 taken because of population distribution.
[b] Value derived from measurements of South Rongelap.

above that expected from global fallout that originated from nuclear weapons' tests in other nations, e.g., Nevada (USA), Russia, China, French Polynesia, and Australia, as well as the Marshall Islands. The ratio of the ^{137}Cs deposited on the atolls from regional fallout (i.e., radioactive deposition that moved directly from Bikini and Enewetak Atolls without global circulation) to that from global fallout is given in Table 2 (as adapted from Simon and Graham 1994).

The ratio of regional to global fallout deposition was specified in Simon and Graham (1994) as a range because of spatial variation and measurement and estimation uncertainty. We used the mean value of the reported range as an independent variable to investigate relationships with the occurrence of nodular disease. The mean value of the ratio should be understood to only be a measure of the long-lived radioactive component that is in excess of that expected from global sources. Because the exposure from ^{137}Cs and other long-lived radionuclides is not specific to the thyroid gland, this measure of radioactive contamination can only be used as a proxy variable to the short-lived radioiodines; however, it may be more relevant than distance from Bikini.

Two different associations were examined using the ^{137}Cs data: (1) the relationship between the excess ^{137}Cs deposition and the distance from Bikini Atoll; and (2) the prevalence of both total number of nodules and of palpable nodules and the mean excess ^{137}Cs ratio for each atoll in which study participants lived in 1954.

Assumptions for the various statistical tests were examined to determine the reliability of test results. These inspections included use of the Shapiro-Wilks' test to examine normality of variables used to determine correlations. In some cases, the Spearman correlation coefficient, a non-parametric equivalent of the Pearson correlation coefficient, was also estimated. Assumptions necessary for reliable regression were also examined including inspection that the prediction error was unrelated to the predicted value.

RESULTS

Population and summary disease data

Between 15 January and 5 March 1993, 1,368 persons were examined; among those were 1,129 born before 1965. In the follow-up examinations held in Ebeye in early 1996, an additional 193 Marshallese born before 1965 were examined. Of the Marshallese examined in Ebeye in 1993 and 1996, 815 were born before the BRAVO test on 1 March 1954. These 815 persons defined the Ebeye BRAVO cohort and prevalence data derived from that group were used to test the Hamilton hypothesis. Of the Marshallese examined in Ebeye, there were 1,062 born before the end of nuclear testing in the Marshall Islands; that group defined the EOT cohort. There were an additional 260 individuals born after the end of nuclear testing and they defined the AT cohort. Table 3 summarizes the disease statistics for the three cohorts although only statistical hypothesis test results for the BRAVO cohort are reported in this paper.

Of the 815 who fit the age criteria for the Ebeye BRAVO cohort, there were 338 males and 477 females; the ratio of male to female was 0.71:1. The minimum age by definition for inclusion into the Ebeye BRAVO cohort was 38 y; the mean age of the participants was 51.1 ± 10.4 y.

In the Ebeye BRAVO cohort, there were 191 (23.4%) persons diagnosed as having a benign solitary nodular goiter and 45 (5.5%) as having a benign multiple nodular goiter (see Table 3). In addition, 15 persons (1.8%) had thyroid cancer. The prevalence of nodular goiter for the entire population was 32.6%.

In the Ebeye EOT cohort, there were 230 (21.7%) persons diagnosed as having a benign solitary nodular goiter and 53 (5.0%) as having benign multiple nodular goiter (Table 3). In addition, 16 persons (1.5%) had thyroid cancer. The prevalence of nodular goiter among the entire cohort was 29.8%. In the Ebeye EOT cohort, the number of disease cases was larger than in the BRAVO cohort presumably due to the additional persons who qualified for inclusion in the EOT cohort. The prevalence in this cohort, however, was slightly lower than in the BRAVO cohort. The prevalence of nodular disease in the AT cohort was very much lower although the crude prevalence of cancer was not greatly different for women. Because the number of people examined in the AT cohort was significantly less, there were correspondingly less cases and, consequently, the disease rates are more uncertain.

Table 3. Diagnostic results of Ebeye BRAVO cohort, Ebeye EOT cohort and Ebeye AT cohort. Absolute numbers and prevalence rates (%).

	Males (%)	Females (%)	Total (%)
BRAVO cohort			
Benign solitary nodular goiter	62 (18.3)	129 (27.0)	191 (23.4)
Benign multiple nodular goiter	12 (3.6)	33 (6.9)	45 (5.5)
Thyroid cancer	5 (1.5)	10 (2.1)	15 (1.8)
Previous thyroidectomy	3 (0.9)	12 (2.5)	15 (1.8)
[w/cancer]	[0]	[3]	[3]
Total nodular goiter	82 (24.3)	184 (38.6)	266 (32.6)
[palpable nodules only, %]	[38, 11.2%]	[93, 19.5%]	[131, 16.1%]
Total cases of cancer[a]	5 (1.5)	13 (2.7)	18 (2.2)
Size of study population	338	477	815
EOT cohort			
Benign solitary nodular goiter	69 (16.1)	161 (25.4)	230 (21.7)
Benign multiple nodular goiter	12 (2.8)	41 (6.5)	53 (5.0)
Thyroid cancer	5 (1.2)	11 (1.7)	16 (1.5)
Previous thyroidectomy	4 (0.9)	14 (2.2)	18 (1.7)
[w/cancer]	[0]	[3]	[3]
Total nodular goiter	90 (21.0)	227 (35.9)	317 (29.8)
[palpable nodules only, %]	[40, 9.3%]	[112, 17.7%]	152, 14.3%]
Total cases of cancer[a]	5 (1.2)	14 (2.2)	19 (1.8)
Size of study population	429	633	1062
AT cohort			
Benign solitary nodular goiter	4 (4.3)	18 (10.8)	22 (8.5)
Benign multiple nodular goiter	1 (1.1)	4 (2.4)	5 (1.9)
Thyroid cancer	—	4 (2.4)	4 (1.5)
Previous thyroidectomy	—	1 (0.6)	1 (0.4)
[w/cancer]		[0]	[0]
Total nodular goiter	5 (5.4%)	27 (16.2)	32 (12.3)
[palpable nodules only, %]	[0]	[11, 6.6%]	[11, 4.2%]
Total cases of cancer[a]	—	4 (2.4)	4 (1.5)
Size of study population	93	167	260

[a] Total cases of cancer = number of diagnosed cancers + cancers in previous thyroidectomies.

Palpable nodules

In the 1993 phase of the study, there were 1,275 Marshallese examined who were born before 1968. Of that group, 68 individuals had palpable nodules upon the first physical examination. However, 8 of those were not confirmed by ultrasound performed immediately after the physical examination. Conversely, after determining the presence and location of a nodule by ultrasound, a second palpation of the patient (supine position with hyperextended neck) revealed an additional 63 palpable nodules. Thus, the total number of palpable nodules was determined as $68 - 8 + 63 = 123$ ($123/1275 = 9.7\%$). The number of cases of nodules identified only by ultrasound (i.e., not-palpable even after a second physical exam) was 151 (11.8%). The ratio of non-palpable to palpable nodules was 1.24:1, and the total number of nodule cases was 274 (21.5%). The crude prevalence of palpable and non-palpable nodules by year of birth for participants in the Ebeye study is summarized in Table 4.

Of the 123 subjects with palpable nodules, 121 had a FNA biopsy; two refused. The success rate of FNA slides was 70%, disappointingly low. In most cases, failure was due to insufficient material aspirated during the single pass through the thyroid, however, in some cases, the quality of the staining was also to blame.

At the follow-up examination in 1996, we sought to re-examine all of the 274 nodule cases identified in 1993. However, in the intervening 3 y, 16 persons of that group had died (in no case was thyroid disease an obvious factor contributing to death), 11 had moved out of the Marshall Islands, and 20 had moved to other atolls and, therefore, had no opportunity to attend the follow-up clinic. Of the remaining 226 people with a nodule diagnosis, we re-examined 192 (85% of those remaining, 70% of the original group).

The same methods and equipment were used as in 1993 except for the improvement in obtaining FNAs. Using the on-site cytologist at the follow-up exams, we performed 84 FNA biopsies of previously assayed patients and achieved a 96% success rate for satisfactory slides.

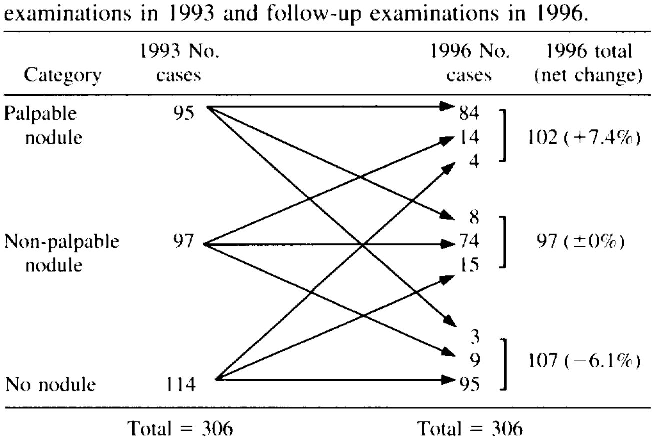
Two of the goals of the re-examinations—confirming the 1993 findings and a study of the progression or regression of thyroid nodules—were viewed as closely

Table 4. Prevalence of palpable and non-palpable nodules and of suspected thyroid cancer in different birth cohorts.

Year of birth	Number of subjects	Non-palpable nodules (%)	Palpable nodules (%)	Suspected cancers (%)
Males				
<1923	36	14 (38.9)	6 (16.7)	2 (5.6)
1923–1928	20	3 (15.0)	1 (5.0)	0
1929–1933	28	2 (7.1)	3 (10.7)	0
1934–1938	20	1 (5.0)	2 (10.0)	1 (5.0)
1939–1943	33	1 (3.0)	7 (21.2)	2 (6.1)
1944–1948	57	3 (5.3)	6 (10.5)	0
1949–1953	97	12 (12.4)	2 (2.1)	1 (1.0)
1954–1958	68	4 (5.9)	2 (2.9)	0
1959–1963	74	3 (4.1)	0	0
1964–1968	73	2 (2.7)	0	0
>1969	20	0	0	0
Males born before 1969	506	0	0	0
Females				
<1923	36	14 (38.9)	6 (16.7)	3 (8.3)
1923–1928	32	6 (18.8)	7 (21.9)	0
1929–1933	38	6 (15.8)	11 (28.9)	0
1934–1938	47	10 (21.3)	7 (14.9)	0
1939–1943	46	12 (26.1)	4 (8.7)	0
1944–1948	99	15 (15.2)	12 (12.1)	2 (2.0)
1949–1953	121	10 (8.3)	22 (18.2)	5 (4.1)
1954–1958	133	21 (15.8)	13 (9.8)	1 (0.8)
1959–1963	114	10 (8.8)	6 (5.3)	2 (1.8)
1964–1968	103	2 (1.9)	6 (5.8)	3 (2.9)
>1969	62	0	0	0
Females born before 1969	769	0	0	0
Total <1969	1275	151 (11.8)	123 (9.7)	22 (1.7)

related. By comparing the 1993 and 1996 examination findings for at least a subset of the study participants, data could be collected for both purposes. Upon re-examination in 1996, some changes in diagnoses were evident as compared to the 1993 findings, though, in general, the original diagnoses were confirmed. We believe that the different diagnoses in 1996 are evidence of changes in the individual's pathology during the intervening period rather than mistaken diagnoses. Table 5 shows the changes in diagnoses in a group of 306 study subjects who were examined on both occasions. In this subset of the 1993 study population, there were roughly equal numbers in the palpable, non-palpable (only ultrasound detection), and no nodule categories: 95, 97, and 114, respectively.

Table 5. Changes in thyroid nodule diagnoses between first examinations in 1993 and follow-up examinations in 1996.



Of the 95 palpable nodule cases in 1993, 84 (88%) remained palpable in 1996. Three of the 95 cases (3.2%) were not detectable by any means in the follow-up exam, and 9 cases (9.3%) became detectable by ultrasound only. Of the 97 cases with a non-palpable nodule in 1993, 74 (77%) remained non-palpable in 1996; 9 of the 97 cases (9.3%) showed no evidence of a nodule in the follow-up exam; but 14 cases (14.6%) had developed into a palpable lesion. Of the 114 cases who had no nodule in 1993, 15 (13.2%) were found to have a non-palpable nodule in 1996 and 4 (3.5%) were found to have a palpable lesion.

The rates of palpable nodules within all three cohorts are of interest for the purpose of intercomparison as well as for comparison with other studies. Summary of all the Ebeye data (see Table 3) show that nodules were found by palpation of the thyroid gland in 131 persons from the BRAVO cohort (131/815 = 16.1%), 152 persons from the EOT cohort (152/1062 = 14.3%), and 11 persons from the AT cohort (11/260 = 4.2%). The ultrasonography found nodular goiter, which was not palpable in a total number of 134 persons (16.4%) from the BRAVO cohort, 165 persons (15.5%) from the EOT cohort, and 21 persons (8.1%) from the AT cohort.

Cancer diagnoses

Clinical diagnoses of cancer were made, where possible, in all examinations. In 22 study subjects diagnosed with palpable nodules in 1993, the ultrasound image was suggestive of cancer or large follicular adenomas, which by ultrasound imaging are indistinguishable from follicular thyroid cancer. We used the diagnostic criteria published by the Japan Society of Ultrasonics in Medicine (1992) with particular emphasis placed on boundary posterior echo, shape and prethyroid muscle echo (Suzuki et al. 1994).

Twelve of the 22 cases were operated in Majuro although histopathological verification is available in only 11 of the 12 operated cases. Table 6 lists these cases together with the results of the 1993 FNA biopsies or the histopathology where available. Of the eleven operated in 1994, there were 3 follicular carcinoma, 5 papillary carcinoma, 2 micropapillary carcinoma, and 1 adenomatous goiter. One additional case was operated in Honolulu in 1996, and it was also papillary cancer. In view of the precision of the ultrasound diagnoses and the im-

Table 6. Ultrasound findings, FNA results and histopathology of suspected and confirmed cancer cases.

ID	Sex	Age	Cohort	Ultrasound findings	FNA results 1993	FNA results 1996	Histopathology	Clinical status
230	F	24	AT	suspicious of cancer	insufficient	follicular adenoma	—	surgery deferred due to pregnancy, planned for 1996
1067	F	29	AT	suspicious of cancer	papillary cancer	N/A	micropapillary cancer	operated Majuro 1994
273	F	29	AT	suspicious of cancer	papillary cancer	N/A	papillary cancer	operated Majuro 1994
123	F	31	AT	large follicular neoplasm, 60 mm	follicular tumor	N/A	follicular cancer	operated Majuro 1994
885	F	31	AT	suspicious of cancer	insufficient	N/A	follicular cancer	operated Majuro 1994
1273	F	39	BRAVO, EOT	suspicious of cancer	insufficient	N/A	papillary cancer	operated Honolulu 1996
877	F	39	BRAVO, EOT	20 mm follicular neoplasm	follicular neoplasm	follicular adenoma	—	deferred for acute medical problems, planned for 1996
1112	F	40	BRAVO, EOT	suspicious of cancer	papillary cancer	N/A	papillary cancer	operated Majuro 1994
501	F	42	BRAVO, EOT	suspicious of cancer	insufficient	adenomatous goiter	—	inoperable for medical reasons
1201	F	46	BRAVO, EOT	suspicious of cancer	insufficient	N/A	papillary cancer	operated Majuro 1994
510	F	57	BRAVO, EOT	suspicious of cancer	papillary cancer	—	—	surgery deferred, planned for 1996
792	F	66	BRAVO, EOT	30 mm follicular neoplasm	insufficient	follicular adenoma	—	inoperable for medical reasons
293	F	71	BRAVO, EOT	suspicious of cancer	papillary cancer	papillary cancer	—	inoperable for medical reasons
315	F	71	BRAVO, EOT	suspicious of cancer	insufficient	papillary cancer	—	inoperable for medical reasons
221	F	72	BRAVO, EOT	suspicious of cancer	follicular neoplasm	N/A	follicular cancer	operated Majuro 1994
83	F	73	BRAVO, EOT	large follicular neoplasm	insufficient	follicular adenoma	—	growing
756	M	39	BRAVO, EOT	suspicious of cancer	insufficient	N/A	micropapillary cancer	operated Majuro 1994
799	M	40	BRAVO, EOT	large follicular neoplasm	follicular adenoma	N/A	adenomatous goiter	operated Majuro 1994
576	M	53	BRAVO, EOT	suspicious of cancer	adenomatous goiter	N/A	papillary cancer	operated Majuro 1994
609	M	55	BRAVO, EOT	suspicious of cancer	adenomatous goiter	N/A	papillary cancer	operated Majuro 1994
272	M	56	BRAVO, EOT	35 mm follicular	papillary cancer	adenomatous goiter	—	growing despite T4 therapy
995	M	75	BRAVO, EOT	50 mm follicular neoplasm	follicular neoplasm	—	—	died from unrelated cause

proved FNA data of 1996, there is evidence to indicate that the total number of cancers in this study group is about 15 or 1.2% (15/1275) of the Marshallese examined or about 12% (15/123) of all the palpable nodule cases we investigated.

Fifteen study participants in 1993 had a neck scar on their first examination that revealed that they had been previously operated for thyroid disease. Historical records indicated that two of the fifteen were members of the Rongelap community who had been directly exposed on Rongelap to the BRAVO test fallout and who had been operated on for thyroid adenomas more than 25 y earlier.

In order to estimate the total cancer rate in this population, the cancers among those previously operated have to be added to those confirmed in our study. An extensive search for histopathology reports in the medical records in the hospitals of Ebeye and Majuro for the 15 earlier operated cases provided evidence that there were two thyroid cancers and one case of occult papillary cancer in adenomatous goiter. Therefore, for further calculations we assume that the total number of thyroid cancers in our study population (n = 1,322) is between 15 and 20, i.e., 1.1 to 1.5%. All but 3 occurred in women; thus, the frequency in female Marshallese is approximately 2%. One of the cancer patients we investigated had been exposed to early fallout of the BRAVO test on Rongelap.

Hypothesis testing

A number of statistical tests were conducted specific to the objectives outlined earlier. To test the hypothesis that there was no difference in prevalence of thyroid nodules among the atolls, a Chi-squared test was carried out. All atolls were used with the exception of Rongelap and Utrik and three atolls (Kili, Mili and Wotho) where the number of persons was less than 10. The null hypothesis was not accepted ($\chi^2 = 34.9$, df = 15, $p < 0.003$). The rejection of this hypothesis prompted further examination into the differences between the atolls and to determine whether there was evidence for a functional relationship between prevalence and distance.

The age-adjusted prevalences were plotted against the distance to Bikini for the total number of nodular goiters and for palpable nodules only. This examination was conducted for the data of both sexes pooled as well as the data for men and women separately. The prevalence were weighted as described earlier. The correlations are listed in Table 7.

There were several unexpected results from these analyses. The correlation of age-adjusted prevalence with distance from Bikini for all nodular goiter with both sexes pooled was not significant for the atolls represented in the Ebeye study ($r = -0.29$, $p = 0.12$) but had a higher correlation and attained marginal significance for the atolls used by Hamilton ($r = -0.43$, $p = 0.07$) (see Table 2 for a listing of the atolls used in the Ebeye study and the Hamilton study). Furthermore, the correlation of age-adjusted prevalence with distance from Bikini for all nodular goiter in males was significant ($r = -0.44$, $p = 0.04$) but was not significant for females ($r = -0.18$, $p = 0.25$).

The correlations for palpable nodules differed from the case of all nodular goiter. The relationship with men and women pooled was close to significance for the Ebeye atolls ($r = -0.37$, $p = 0.06$) and the atolls used by Hamilton ($r = -0.43$, $p = 0.08$). Fig. 1 shows a plot of the relationship between palpable nodules and distance from Bikini. The key to the numbered atolls in this figure is provided in Table 2.

In order to examine the occurrence of nodular goiter in more detail, a logistic regression analysis was conducted. As in Hamilton's study, the variable θ was initially included in addition to distance to better define the location of each residence atoll with respect to Bikini (see Table 2). The logistic regression was first run with all prediction terms, thereafter sequentially eliminating those with p-values greater than 0.10. The analysis was carried out for the four combinations of all nodular goiters, palpable nodules only, atolls from the Ebeye study and atolls from the Hamilton study.

In the analyses that we conducted, neither the interaction term between θ and distance or the independent variable θ were statistically significant. In the regression model using data for all nodular goiters, the variable distance was not significant and, therefore, excluded. However, distance maintained significance for the Hamilton atolls. For the analysis of palpable nodules only, distance remained in the model for both the Ebeye atolls and the Hamilton atolls. The variables sex as well as age were both significant predictors of the presence of

Table 7. Correlations between age-adjusted nodule prevalence and distance from Bikini. Correlation coefficients are Pearson's r (weighted) except where noted in brackets [. . .] which are Spearman's r (unweighted). Atolls are either: (1) all the residence atolls in 1954 for subjects in the Ebeye study, or (2) all the residence atolls in 1954 for subjects in Hamilton et al. (1987) study.

Diagnosis	Atolls	Sex	r	p-value
All nodular goiter	those in Ebeye study	M & F	−0.29[−0.34]	0.12[0.14]
All nodular goiter	those in Hamilton study	M & F	−0.43[−0.38]	0.07[0.19]
All nodular goiter	those in Ebeye study	M	−0.44	0.04
All nodular goiter	those in Ebeye study	F	−0.18	0.25
Palpable nodules only	those in Ebeye study	M & F	−0.37[−0.45]	0.06[0.04]
Palpable nodules only	those in Hamilton study	M & F	−0.42[−0.41]	0.08[0.14]
Palpable nodules only	those in Ebeye study	M	−0.14	0.32
Palpable nodules only	those in Ebeye study	F	−0.44	0.06

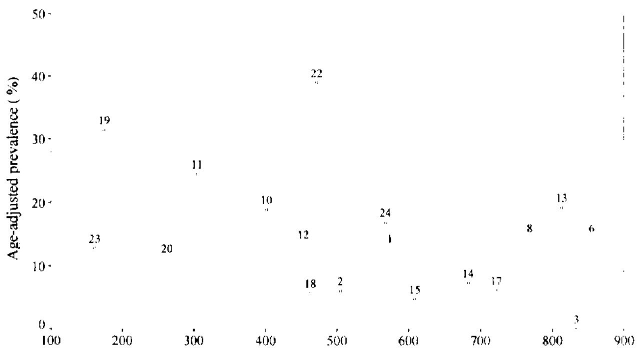


Fig. 1. Age-adjusted prevalence of palpable nodules as a function of distance (km) of residence atolls in 1954 from Bikini Atoll. All atolls of Ebeye study are included. Atoll identification numbers refer to Table 2.

nodular goiter in general and for the presence of palpable nodules. For sex, the odds ratio (female to male) varied from 2.02 to 2.24 within the four variable combinations examined. These findings are summarized in Table 8.

DISCUSSION

Most previous population screening programs to detect nodular thyroid disease, e.g., the follow-up of the exposed Marshallese by medical teams organized by Brookhaven National Laboratory (Conard 1984; Adams et al. 1989) and the study of Hamilton et al. (1987) have used palpation of the neck as the primary criterion of positive findings. The development of high resolution ultrasound equipment permits the additional means for objective and precise thyroid and nodule size determination and the ability to photographically document abnormalities for later study. One of the achievements of this study was establishing the capability and value of using ultrasound in a large scale study and in remote and primitive environments. Some of the examinations in this study were conducted on remote islands without centralized electrical power. Using a portable gasoline powered generator as small as a few kW power, ultrasound was used in the field without any reduction in diagnostic quality. Whereas the advantages of this method are several, there remains the question of the clinical importance of nodules that are not palpable.

Several findings of the clinical examinations were noteworthy. First, non-palpable nodules tended to be smaller than palpable nodules; the median diameter being 7.5 mm for non-palpable compared to 16 mm for palpable. The size distributions of the palpable and non-palpable nodules, however, showed considerable overlap (Fig 2). For example, 20% of palpable nodules were smaller than 10 mm diameter while 20% of non-palpable nodules were larger than 10 mm.

We defined the palpability of thyroid nodules to be the proportion of all nodules detected by ultrasound that were also palpable. The palpability increased only very slowly with increasing size as measured by ultrasound (Fig. 3). Furthermore, in 52 women who had nodules of 9 to 12 mm diameter, 40% of which were palpable, there was no correlation of palpability with a body mass index. In this group, palpability of nodules for obese women (17 of 28 cases) was similar to that for normal and slim size women (15 of 24 cases). Although neck size and the amount of adipose tissue over the thyroid is often speculated to be related to the difficulty in palpating a nodule, those generalizations were not well supported by our observations.

The ease of palpation of a nodule is determined partially, but not exclusively, by the size of the nodule.

Table 8. Results of logistic regression, independent variables with $p < 0.10$.

	Atolls of Ebeye study		Atolls of Hamilton study	
	All nodules	Palpable nodules only	All nodules	Palpable nodules only
Age				
Coefficient β	0.0437	0.0215	0.0422	0.0273
p-value	<0.0000	0.019	<0.000	0.007
Standard error	0.0074	0.0091	0.0084	0.01
95% confidence interval on β	0.029–0.059	0.003–0.04	0.025–0.059	0.007–0.047
Sex				
Coefficient β	0.769	0.702	0.806	0.723
p-value	<0.000	<0.001	<0.000	0.002
Standard error	2.16	2.02	2.24	2.06
95% confidence interval on β	1.56–3.00	1.33–3.07	1.54–3.26	1.29–3.29
Distance				
Coefficient β	ns	−0.001	−0.0012	−0.0014
p-value	ns	0.084	0.04	0.073
Standard error	ns	0.0006	0.0006	0.0008
95% confidence interval on β	ns	−0.002–0.000	−0.002–0.000	−0.003–0.000
Constant				
Coefficient β	−3.464	−2.7068	−2.8632	−2.853
p-value	<0.000	<0.000	<0.000	<0.000
Standard error	0.4228	0.626	0.574	0.7012
95% confidence interval on β	−4.31/−2.618	−3.959/−1.455	−4.011/−1.752	−4.255/−1.451

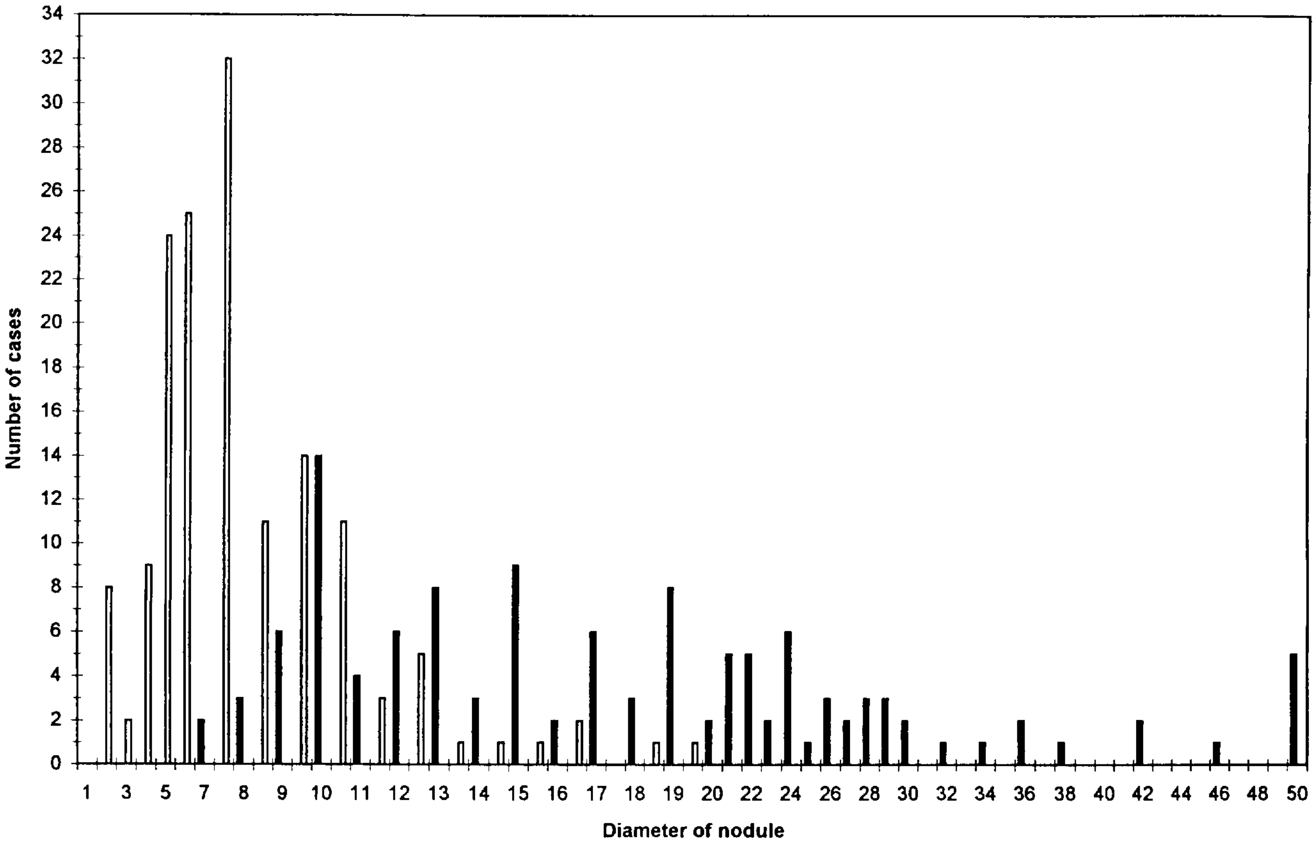


Fig. 2. Size distribution of palpable (closed bars) and non-palpable (open bars) nodules for subjects examined at Ebeye. The diameter is defined as the largest diameter of the largest nodule of a study subject in mm.

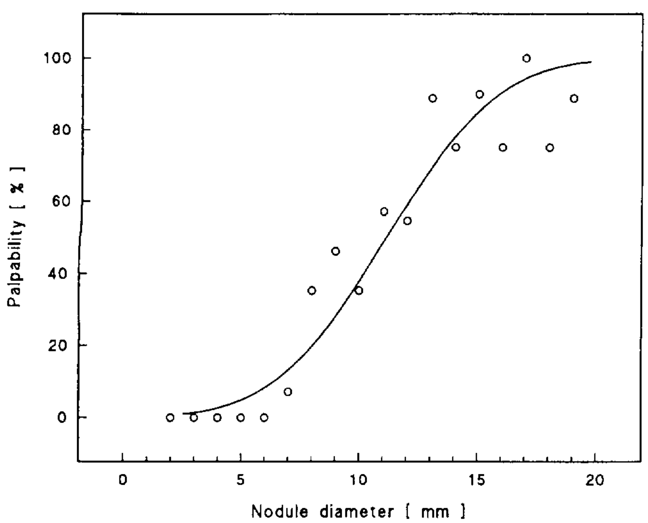


Fig. 3. Palpability of nodules as a function of its largest diameter in mm.

The probability of a successful palpation does increase with nodule size though there are also other important factors including the specific anatomy of each patient's thyroid, neck, and skin as well as the experience and expectations of the examiner. Although the experience of the endocrine surgeons who made the examinations was very extensive, false positive and false negative judgments sometimes occurred. For example, about 12% of nodules palpated during the first examination proved to be non-existent on ultrasound imaging. On the other hand, the number of palpable nodules doubled after the examiner had learned about the presence and approximate location of a nodule from ultrasound. For this reason, we suggest that in addition to clinical investigation and palpation, high resolution ultrasound imaging is an important addition to accurately determine the nodule prevalence rate in a population that is undergoing screening. The size and the structure of a thyroid nodule is probably more important in regard to its clinical impact than its palpability; however, repeated follow-up of this group of patients will be needed to resolve this question.

Comparison of our 1993 and 1996 findings demonstrate that the original diagnoses were generally verified. The number of individuals in the non-palpable category did not change over the 3-y period though there was some cross-over of individuals between categories (see Table 5). During the 3-y interval, the palpable and no nodule category were about equally stable though the change in number of palpable nodules was towards an increase (+7%) while the change in number of cases without any nodule was towards a decrease (−6%). On an individual basis, a non-palpable nodule was most likely to change (24% changed category), a no nodule case was somewhat less likely to change (17% changed category) and a palpable nodule was the most likely to remain the same (only 10% changed category).

Approximately 9% of the non-palpable nodules disappeared during the 3-y interval (usually cystic lesions of less than 6 mm diameter), and about 9% of palpable nodules became non-palpable. Whereas these numbers may give some indication of the potential error range of the findings of screening programs, particularly those conducted over several years time, a more detailed analysis of the echo patterns is required before we can identify structural features that predict progression or regression of palpable or non-palpable nodules.

The prevalence of palpable nodules we observed in Ebeye (16.2%) was about twice that noted by Hamilton et al. (1987) (6.2% crude prevalence rate). Assuming that the population on Ebeye in 1993 represented a similar cross-section of the population of the Marshall Islands as when Hamilton examined the population 8 y earlier, either the prevalence had significantly increased during the elapsed time, or there were significant differences in diagnostic sensitivity of the two studies. The latter explanation is suggested by the high proportion of thyroid nodules that could only be palpated after they had been diagnosed by ultrasound first. This fact alone could explain the differences in numbers of detected nodules between the two screening programs and further emphasizes the usefulness of ultrasound to determining an accurate assessment of palpable nodular disease within a population.

Fine needle aspiration biopsy of palpable nodules remains the gold standard of diagnosis for nodules. However, in this field study, which routinely operated under tropical and sometimes primitive conditions, the rate of insufficient material or insufficient staining was high. On the other hand, even under these difficult conditions, the accuracy of the ultrasound diagnosis of cancer was >90%, remarkably high as judged from the agreement with the histopathological evidence from the operated cases.

In 4 cases in 1993 that were suggestive of cancer by the ultrasound examination but that were not operated, FNA was able to provide a cytological diagnosis in 1996. A strong likelihood of cancer was noted for 2 cases and follicular adenoma in 1 case. In the 4 cases that were diagnosed by ultrasound as follicular adenoma, 3 were diagnosed by FNA as adenoma. In 2 of 42 cases where the ultrasound diagnosis in 1993 was adenomatous goiter, FNA biopsy in 1996 was indicative of cancer.

Taking histological or cytological diagnosis as a criterion, sensitivity of ultrasound diagnosis was 87% and specificity was 96%. Overall, these data demonstrate that in the hands of experienced physicians who make their diagnosis during the conduct of the examination, ultrasound is nearly equivalent to FNA biopsy in its ability to determine the nature of a thyroid nodule.

Comparison with cancer rates elsewhere

The thyroid cancer rate in our study was not dissimilar to that observed in 2,587 atomic bomb survivors in Nagasaki where 21 cancers were reported (0.8%) compared to 1 in 935 (0.1%) unexposed persons (Nagataki et al. 1994). A cancer rate in unexposed adult women screened in Kamaishi, Japan, was 0.6% (Takaya et al. 1982), intermediate to the Nagasaki control and exposed population rates.

Cancer statistics from different countries suggest great differences in thyroid cancer incidence (IARC 1992). In particular, rates are high among island populations (Henderson et al. 1985; Kolonel et al. 1990; IARC 1992) including Hawaii, Iceland and New Zealand. For example, one of the highest reported rates is for Filipinos living in Hawaii (Goodman et al. 1988); thyroid cancer among that group accounted for 2.7% of all non-skin cancers in Hawaii between 1973 and 1977. Native Hawaiians and those of Chinese descent who live in Hawaii have also shown high rates. A similarly high rate was reported to be nearly 2% among female Melanesians over 25 y of age (Ballivet et al. 1995). The thyroid cancer prevalence in female Marshallese is similar to these values.

The likelihood of an enhancement in the nodule and cancer rates in this study, relative to most reported rates, was considered as a result of our intensive screening. That phenomenon was demonstrated by Ron et al. (1992) who reported a 7-fold increase in cancer rates and a 17-fold increase in nodule rates when screening followed public announcements for examinations and publicity concerning the relationship of thyroid disease to head and neck irradiation. Due to our screening efforts, some enhancement of the cancer rate has certainly occurred relative to most nationally reported thyroid cancer statistics. Presently it is not possible to know the extent of this effect among the Marshallese population. Enhancement of the cancer rate is primarily of concern in making comparisons with cancer rates from other countries. The determination of relationships between disease incidence and location within the Marshall Islands should not be effected by this phenomenon.

In our study, 73% (8/11) of the cancers confirmed by histopathology were of the papillary or micropapillary type; the remaining 27% were of the follicular type. This ratio generally agrees with observations in Hawaii during the years 1960 through 1984, where 74% of thyroid cancers were papillary and 17% were follicular (Goodman et al. 1988).

Correlations with environmental radioactivity

Considerable thought has been given to alternative hypotheses that might explain a decreasing relationship between nodular goiter and distance from the Bikini test site. Hamilton assumed that his results indicated that the geographic extent of radioiodine exposure was broader than assumed and that distance served as a proxy variable for past exposure to short-lived radioiodines. To investigate the plausibility of that hypothesis, we examined recently acquired radioactive contamination data of the

Marshall Islands from a radiological monitoring program of the entire nation (Simon and Graham 1997). Accordingly, we plotted the mean ratio of ^{137}Cs (regional:global deposition) against distance from Bikini (Fig. 4). However, that analysis showed no obvious relationship thus casting some doubt on the existence of a decreasing linear dose effect as a function of distance. Furthermore, we plotted age-adjusted prevalence of all nodular goiters and palpable nodules only against the ratio of ^{137}Cs (regional:global deposition) and, similarly, there was no obvious relationship.

It should be noted that the magnitude of environmental ^{137}Cs is not a perfect proxy variable for radioiodine exposure. The primary determinant of radioiodine air concentrations that might lead to individual exposure is the cloud transit time from the point of the explosion to the inhabited location. Secondary parameters that determine the bioavailability of radioiodine include particle size in the atmosphere, the presence or absence of rain, etc. Variations in transit time among different tests would dramatically affect the radioiodine concentration of the cloud but would have little effect on the ^{137}Cs concentration because of the difference in their physical half-lives. Yet, for locations with near equal transit times, the ^{137}Cs should be highly correlated with the past radioiodine deposition, particularly ^{131}I, the longest lived of the short-lived suite.

We did observe, however, a relationship between the excess ^{137}Cs and angle (as measured clockwise from a E-W line); the relationship decreases in a curvilinear fashion from 0° to about 30° where it levels out at a value of approximately 1.0. This indicates that the cloud's direction of travel was not highly correlated with straight line distance in all directions. It is known, for example, that the cloud likely initially moved in the east direction, but then may have veered southerly with lower air concentrations as a result of dilution and decay. The fact, however, that θ was not significant in the logistic regression lends little support to this variable as an explanatory cause for the pattern in thyroid disease.

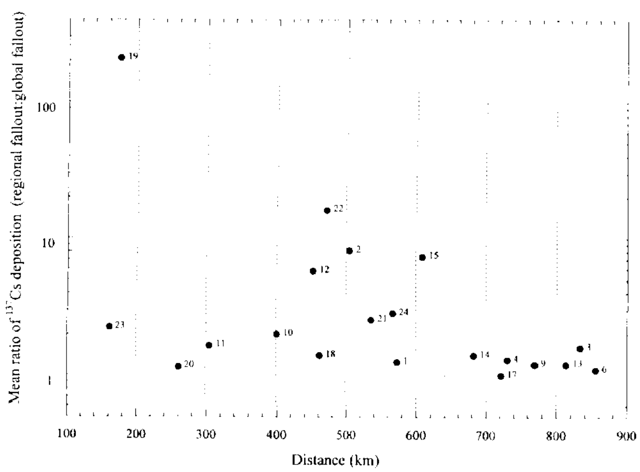


Fig. 4. Mean of regional fallout:global fallout ^{137}Cs deposition in atolls as a function of distance (km) from Bikini Atoll (data from Simon and Graham 1994, 1997).

Diet and other risk factors

A number of risk factors in addition to ionizing radiation may be related to the high cancer rates. There is accumulating evidence that populations resident on island countries, in particular those in the tropical waters of the Pacific, have higher than normal incidence rates for thyroid cancer despite earlier observations of little ethnic difference in rates (Ron and Modan 1982). These observations may be related to diet as well as other factors peculiar to island life.

Diet is considered as a plausible risk factor (Kolonel et al. 1990), in particular, where the consumption of high iodine seafood is common. Seafood based diets have showed positive risk associations to thyroid cancer in a number of studies (Kolonel et al. 1990; Ron et al. 1987; and Preston-Martin reported by Henderson 1990).

SUMMARY AND CONCLUSIONS

The objectives of this study were (1) to examine and gather data on the frequency of thyroid disease (both nodular and cancerous conditions) in as large of proportion as possible of those Marshallese alive during the years of atomic testing, (2) to advise the Government of the Marshall Islands on the findings from the medical screening program, and (3) to test the hypothesis of Hamilton et al. (1987) Goals (1) and (3) are the main subject of this report though several other findings are noteworthy and are also summarized here.

First, non-palpable nodules tended to be smaller than palpable nodules although the size distributions of the palpable and non-palpable nodules show considerable overlap. This finding implies that unassisted palpation may not be successful in finding the smaller nodules, which can be only palpated after directing the physician to the location by ultrasound.

Ultrasound was shown to be a viable technique even in tropical and primitive environments as the devices can be successfully powered by small, portable electrical generators. The advantages of ultrasound are that it can supplement palpation by providing objective measurements of the size of lesions and can photographically record the examination for later review. In the hands of experienced practitioners, ultrasound can nearly equal the reliability of FNA biopsy for predicting a cancerous condition. Comparison of our findings from the 1993 and 1996 examination phases demonstrated that the original diagnoses were generally verified.

The prevalence of palpable nodules was highest in the Ebeye BRAVO cohort (16%), about 20% lower in the EOT cohort, and about 85% lower in the AT cohort. Most of the difference in the AT cohort is undoubtedly due to their younger age, though the difference is dramatic enough to suggest that other factors might be involved. Radiation exposure may be one of several factors involved.

The prevalences of non-palpable nodules were similar among all three age cohorts but were moderately

Table 9. Comparison between study of Ebeye BRAVO cohort and Hamilton et al. (1987). Results are given for palpable nodules only except where noted and for those atolls which were included in each study.

	Ebeye BRAVO cohort	Cohort of Hamilton et al. (1987)
Size of cohort	815	2,273
Location of study	Ebeye Island, Kwajalein Atoll	Present day residence atolls
Proxy variable for radioiodine exposure	Residence in 1954; present day environmental ^{137}Cs measurements	Residence in 1954
Number of residence atolls of study subjects in 1954	21	14
Description of medical examinations	Palpation, ultrasonography, FNA biopsy, histology	Palpation
Definition of thyroid nodule	Visibility on ultrasound, solitary/multiple	solitary, palpable, >1.0 cm diameter
Crude prevalence rate	16.2	6.2
Range of prevalence of palpable nodules exclusive of Rongelap and Utrik (%)	0–36.4	0.9–10.6
Estimate of prevalence in Mili and Ebon Atolls (%)	12.5 (4/32)	2.45 (9/370)
Odds ratio female/male	2.1	3.7
Chi-square test of homogeneity in prevalence among atolls exclusive of Rongelap and Utrik	$\chi^2 = 34.9$; df = 15, $p < 0.003$ (all nodules)	$\chi^2 = 23.45$, df = 11, $p < 0.025$
Pearson correlation coefficient between age-adjusted prevalence (weighted) and distance from Bikini	$r = -0.42$ ($p = 0.08$) for Hamilton atolls; $r = -0.37$ ($p = 0.06$) for all atolls of Ebeye cohort	$r = -0.65$, $p < 0.002$
Statistically significant predictor terms in logistic regression model	Age, sex, distance ($p = 0.07$)	Age, sex, distance, θ, distance θ

different from palpable nodule rates in the EOT and AT group. The rate of non-palpable lesions was virtually the same in the BRAVO cohort (16%) as for palpable nodules, about 10% higher in the EOT cohort, and about twice as high in the AT cohort. This availability of such data is uncommon and is undoubtedly valuable as a description of the progression of thyroid disease with age in an island population.

The prevalence of palpable nodules that we observed in Ebeye (16.2%) was more than twice that noted by Hamilton et al. (1987) (6.2% crude prevalence rate) when averaged over all the atolls of residence in 1954. The use of ultrasound to direct physicians in locating and palpating nodules is the primary explanation for the differences in the two screening programs, aging of the population being a secondary cause.

The results of statistical analysis and hypothesis testing for the population in this study are suggestive of relationships similar to that observed by Hamilton et al (1987). A summary of the results from the Ebeye analysis and the analysis of Hamilton et al. is shown in Table 9. Because of the suggestion that location of residence during the testing era may be related to nodule prevalence, further analysis of the incidence and casual factors of thyroid disease among Marshallese appears to be a worthwhile endeavor.

An examination of the relationship between present day ^{137}Cs concentrations in the environment and distance from the Bikini test site did not shed any light on radioactive contamination as a causal factor. No relationship was obvious between the variables examined although it is understood that only for locations of equal fallout transit time would the radioiodine concentrations be expected to be highly correlated with cesium.

Though we were not able to confirm the Hamilton hypothesis with a high level of statistical significance, there is also no evidence to disprove it. Moreover, our data on nodule prevalence with distance show similar trends to those observed by Hamilton. Our interpretation is different, however, in that we found present levels of ^{137}Cs and distance to show no relationship which is suggestive of radiation exposure as a causal factor. Two possibilities to explain this phenomenon might be considered. The first deserves the most attention because it is the most plausible: (1) even though there is no relationship between cesium levels and distance, there may be a functional relationship between radioiodine exposure and location though it very well might not be a relationship that is linear with distance; or (2) there is another phenomenon that is responsible for induction of thyroid abnormalities, and it is also distance dependent. It is difficult to conceive of plausible risk factors that might be distance dependent though the influence of diet and dietary (stable) iodine intake must be considered. Either iodine deficiency or excess might be responsible for unusual thyroid responses in island inhabitants. If, for example, the intake of seafood differed among the atolls because of differences in fish availability, a deficiency might have been occurred in one group relative to another. In some other atolls, an excess might have occurred for the opposite reasons. Such hypotheses require further study.

Presently, we believe that it is reasonable to proceed with our current plans of reconstruction of exposures to the individuals we have examined for thyroid disease in the Marshall Islands. Such an effort will necessarily rely on residence history data for each individual and historcal monitoring data, which will require both careful interpretation and probably some degree of interpolation to cover all locations and all time periods. Until such detailed examinations are complete, the cause of high rates of thyroid nodules and cancer and their relationship with locations of residence remains without adequate explanation.

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